# PATENT COOPERATION TREATY



# PCT

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>P-INCI-X-04-0273 | **FOR FURTHER ACTION** See Form PCT/IPEA/416 | |
|---|---|---|
| International application No.<br>PCT/EP2004/008510 | International filing date *(day/month/year)*<br>29.07.2004 | Priority date *(day/month/year)*<br>30.07.2003 |
| International Patent Classification (IPC) or national classification and IPC<br>A61K31/4045, C07D209/08, C07D409/12, C07D513/04, A61K31/429, A61P3/04 | | |
| Applicant<br>LABORATORIOS DEL DR. ESTEVE S.A. et al. | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 28.02.2005 | 30.06.2005 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Telephone No. +49 89 2399- |

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

International application No.
PCT/EP2004/008510

**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   **Description, Pages**

   1-66 as originally filed

   **Claims, Numbers**

   1-73 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

   * *If item 4 applies, some or all of these sheets may be marked "superseded."*

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-73 |
| | No: | Claims | 1, 6-9 |
| Inventive step (IS) | Yes: | Claims | 2-24 |
| | No: | Claims | 1-73 |
| Industrial applicability (IA) | Yes: | Claims | 1-73 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. **Reference is made to the following documents:**

D1: WO 03/042175 A (ESTEVE LABOR DR) 22 May 2003 (2003-05-22)
D2: EP-A-0 815 961 (WABAG WASSERTECHN ANLAGEN GMBH) 7 January 1998 (1998-01-07)
D3: WO 02/060871 A (FLAUGH MICHAEL EDWARD ; GILLIG JAMES RONALD (US); HEINZ LAWRENCE JOSEP) 8 August 2002 (2002-08-08)
D4: US-A-3 472 870 (GOULD BARBARA E ET AL) 14 October 1969 (1969-10-14)
D5: BROWN F J ET AL: "Evolution of a Series of Peptidoleukotriene Antagonists: Synthesis and Structure-Activity Relationships of 1,6-Disubstituted Indoles and Indazoles" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 6, no. 33, 1990, pages 1771-1781, XP002077393 ISSN: 0022-2623

2. **Novelty** (Article 33(1) and (2)PCT)

The present application discloses compounds of formula (Ia-b) (see present Claims 1, 9), which are useful as 5-HT-6 modulators.

The present compounds(see Claims 1 and 9) differ form the D1-D2 compounds on the account of the position 6 of substitution with sulfonamide moiety on the indole ring (instead of the 5-th position for the D1 compounds and 4-th position for the D2 compounds), from the D3 compounds on the account of the sulfonamide moiety (see Claim 1) and from the D4 compounds on the account of the A substituent of the sulfonamide function (which in the present case should contain a (hetero)aromatic ring and in D4 case is an alkyl or alkenyl chain). The D5 compounds differ from the present compounds on the account the N-benzyl moiety from the 1-th position of the indole ring (the present R1 substituent cannot be an aryl moiety). Consequently, the novelty of the present subject-matter is acknowledged.

3. **Inventive step** (Article 33(1) and 33(3) PCT)

The present application discloses 6-sulfonamidoindoles which are substituted on position 1 of the indole with an amino moiety or with a (hetero) cycloaliphatic ring useful as 5-HT-6 modulators.

D1, which is regarded as being the closest prior art, discloses 5-HT-6 modulators which are also sulfonamide indoles. The main differences between the present compounds and the compounds disclosed by D1 are the positions of substitution with the sulfonamide moiety and -(CH2)n-R1 substituent on the indole ring (see present Claim 1 and the Claim 1 of D1).

The problem underlying the present invention cannot be regarded in providing further sulfonamide indoles useful as to treat diseases modulated through the 5-HT-6 receptor, for the following reasons:

D2 discloses 5-HT-6 modulators, which are 4-sulfonamidoindole derivatives (see compounds of formula (Ie)(page 5 and Claim 6 of Do).

D4 disclose indoles which can be substituted with a sulfonamide moiety in any one of the positions 4-7 of the indole and which are useful to treat the same diseases as in the present case. Though D4 does not specifically disclose the role of 5HT-6 receptors, it clearly discloses the same application in terms of disorders to be treated. The possible discovery of a specific mechanism cannot be taken as an objective problem and eventually an inventive step as such.

The present general structures (Ia-b) differ from the compounds disclosed by D1 only in the positions of substitution with the ASO2N- and -(CH2)n-R1 moieties on the indole ring. D2 teaches that compounds substituted in position 4 with a sulfonamide function are useful as 5-HT-6 modulators. D3 discloses 5-HT-6 modulators, which can be substituted with a cycloalkyl moiety on the nitrogen of the indole ring (see e.g. examples 23, 28, 67 of D3) as for the present case.

Having regard the minor modifications between the present compounds and the D1 compounds and in view of the D2-D4, the skilled person would have expected that the same qualitative effect would be maintain in such similar compounds. Moreover, the present R1 substituent can present very different chemical structures and therefore seems not to be relevant for retention of the claimed activity for the present compounds.

The problem underlying the present application should thus be seen in providing of sulfonamide indole derivatives with unexpected or surprising effects compared to those of the closest prior art. An inventive step cannot be recognized as it is not yet shown by appropriate information, e.g. in form of experimental data, that substantially all the claimed compounds have un unexpected property or improved activity over the structurally closest prior art compounds (D1), which is attributable to the distinguishing feature of the invention.